Notice of Allowability	Application No.	Applicant(s)	
	09/718,998	QUEEN ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *amendment filed 3/31/2005*.

2. ☒ The allowed claim(s) is/are *108-117,119,120,122-135,137-172,174-181,183--191,193-201,203-209*.

3. ☒ The drawings filed on *28 June 2004* are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date 3/1/04 and 8/4/03
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *6/3/2005* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

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EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Joe Liebescheutz on June 3, 2005.

The application has been amended as follows:

In the claims:

125. A method of producing a humanized immunoglobulin that specifically binds to an antigen with an affinity constant within about four-fold that of the donor immunoglobulin, comprising the steps of:

(1) selecting an acceptor immunoglobulin heavy chain variable region framework whose sequence is a consensus sequence of human heavy chain variable region framework sequences;

(2) synthesizing a DNA segment encoding a humanized immunoglobulin heavy chain variable region, comprising complementarity determining regions (CDRs) from a donor immunoglobulin heavy chain variable region and the selected acceptor immunoglobulin heavy chain variable region framework;

(3) introducing [a] the DNA segment encoding the humanized immunoglobulin heavy chain variable region and a DNA segment encoding a humanized immunoglobulin light chain variable region into a cell; and

(4) expressing the DNA segments in the cell to produce the humanized immunoglobulin.

129. A method of producing a humanized immunoglobulin that specifically binds to an antigen with an affinity constant within about four-fold that of the donor immunoglobulin, the method comprising:

providing a cell containing DNA segments encoding humanized light and heavy chain variable regions; and expressing the DNA segments in the cell to produce the humanized immunoglobulin;

wherein the cell containing the DNA segments was produced by:

(1) selecting an acceptor immunoglobulin heavy chain variable region framework whose sequence is a consensus sequence of human immunoglobulin heavy chain variable region framework sequences;

(2) synthesizing a DNA segment encoding a humanized immunoglobulin heavy chain variable region, comprising a complementarity determining region (CDR) from a donor immunoglobulin heavy chain variable region and the selected acceptor immunoglobulin heavy chain variable region framework and further comprising amino acids from the donor immunoglobulin heavy chain framework outside the CDRs that replace the corresponding amino acids in the acceptor immunoglobulin heavy chain

variable region framework, at positions in the immunoglobulins where the amino acids are capable of interacting with the CDRs;

(3) introducing [a] the DNA segment encoding the humanized immunoglobulin heavy chain variable region and a DNA segment encoding a humanized immunoglobulin light chain variable region into a cell.

174. A humanized immunoglobulin according to [claim170] claim 170, wherein the amino acid at position H49 has been replaced.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance:

1. The rejections of claims under the judicially created doctrine of obviousness-type double patenting over U.S. Patents 6,180,370, 5,530,101, 5,693,762, and 5,585,089 are withdrawn in view of the terminal disclaimers filed on March 31, 2005.

2. The rejections of claims 125-132 and 198-209 under 35 U.S.C. 112, 2nd paragraph as being indefinite for failing to particularly and distinctly point out the subject matter of the claimed invention is withdrawn upon further consideration.

3. The objection of claims 118, 121, 136, 173, 182, 192, and 202 under 37 C.F.R. 1.75(c) as being of improper dependent form for failing to further limit the subject mater of the previous claim is withdrawn in view of the amendment canceling these claims.

4. The rejection of claims 108, 110, 112-115, 133, 134, 136, 137, 139-141, 143-148, 153, 154, 156-158, 161, 162, 164, 165-168, 170, 171, 173-180, 182-187, 189, 190, 192, 197, 208 and 209 under 35 U.S.C. 102(a) as being anticipated by Riechmann (Riechmann, L. et al., Nature, 332: 323-327, 1988, March) is withdrawn in view of applicants' persuasive arguments. The claims are drawn to humanized immunoglobulins in which at least 3 amino acids from the framework of the acceptor immunoglobulin outside the Chothia and Kabat CDRs are replaced by the corresponding amino acids from the framework of the donor immunoglobulin; or drawn to humanized immunoglobulins having substitutions of amino acids from the acceptor with corresponding amino acids from the donor at specifically identified framework positions that also happen to be outside the Chothia and Kabat CDRs. Applicants argue that the claims should not be view as product-by-process claims because no step is actually performed in which an amino acid from the donor antibody is excised from the donor and introduced into the acceptor framework, and that the term "replace" is a description of the composition of the humanized antibody. Applicants assert that because the term "replace" is properly construed as describing a donor amino acid different from a corresponding acceptor amino acid, all of the claims are distinguished from Riechmann's humanized antibody. The examiner finds the applicants' arguments persuasive because the use of the term "replace" implies that the positions that will be altered in an acceptor framework will be positions where the amino acid in the acceptor

framework differs from the amino acid at the corresponding position in the donor framework. Therefore, the claimed humanized immunoglobulins are distinguished from Riechmann's humanized immunoglobulin because, for Riechmann's humanized antibody, at the positions cited by the examiner in the rejection under 35 U.S.C. 102(a), the amino acids of the acceptor framework do not differ from the corresponding amino acids of the donor framework.

5. The rejection of claims 116, 118, 119, 121-124, 198-200, 202, 204, and 207 under 35 U.S.C. 102(a) as being anticipated by Riechmann (Riechmann, L. et al., Nature, 332: 323-327, 1988, March) as evidenced by Waldmann (U.S. Patent, 5,846,534; issued Dec. 8, 1998; effective filing date Oct. 12, 1989) is withdrawn in view of applicants' persuasive arguments. In view of applicants' statements on the record that the term "consensus sequence" was and is understood in the art to denote the sequence formed from the most frequently occurring amino acids in a family of related sequences, the examiner interprets claims containing the recitation "consensus framework", as properly construed as drawn to immunoglobulins in which the amino acid sequence of the framework comprises a consensus sequence, where the phrase "consensus sequence" means that at each position of the consensus sequence, the amino acid is the amino acid occurring most frequently in a family of related sequences for that position in the sequence. Therefore, the claims are distinguished from Riechmann, even if the light chain used by Riechmann does have a consensus sequence, because the antibody of Riechmann lacks a heavy chain having a consensus sequence, and all of the claims at issue require the presence of at least a heavy chain having a consensus framework.

Change of Inventorship:

In view of the papers filed March 31, 2005, the inventorship in this nonprovisional application has been changed by the deletion of Man Sung Co, William P. Schneider, Nicholas F. Landolfi, and Kathleen L. Coelingh as inventors.

The application will be forwarded to the Legal Instruments Examiner for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 571-1600.

ALH

Anne L. Holleran
Patent Examiner
June 3, 2005

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
6/9/05